

Inventors: Al-Obeidi et al.  
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corrected, "Example XXXVII." Reference is made to an example that teaches proteases that are involved in blood coagulation and the fibrinolysis cascade. Example XXVII at page 66 teaches the preparation of a compound, Ac-pAph-Chg-NHCH<sub>2</sub>-(4-methylpyridinium). Example XXXVII at page 87 teaches proteases involved in blood coagulation and fibrinolysis cascade. As such, the amendment to the specification does not constitute new subject matter.

#### Restriction Requirement

Claims 1 to 23, which are claims drawn to compounds, were restricted in Paper No. 8, mailed November 11, 1999. The restriction of the compound claims was made according to the value of m, that is, where "m = 1" as in claims 1 to 11, or where "m = 0" as in claims 12 to 23. Applicants elected claims 1 to 11 with traverse in Paper No. 10. The restriction requirement was made final in the Office action mailed March 23, 2000 (Paper No. 11), wherein Applicants were informed that the methods of use claims (claims 24 and 25) would be rejoined upon finding of allowability for the respective compounds.

#### Rejoinder of Claims 21, 22 and 23

Applicants upon further review note and submit that claims 21, 22, and 23 should properly be rejoined with claims 1 to 11. Claims 21, 22, and 23 cover specific compounds of the invention where m = 1. Applicants note that claims 18 and 19, in a similar manner, cover specific compounds of the invention where m = 0. Although in this instance, claims 18 and 19 are properly

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grouped with the invention of claims 12 to 17. Applicants respectfully request rejoinder of claims 21, 22, and 23 to the current prosecution of compound claims 1 to 11.

#### Status of Prosecution

The Office action states that currently, claims 1 to 11 are free of the prior art, with which Applicant concurs. Following the restriction requirement, prosecution proceeds to claims 24 and 25 directed to methods of use.

#### Rejections Under 35 U.S.C. 112, First and Second Paragraphs

Claims 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, it is alleged that these claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, specifically, the Office action states that "enablement is lacking regarding the use for the myriad of compounds". Claims 24 and 25 are also rejected under 35 U.S.C. 112, second paragraph, as it is alleged that these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse both rejections.

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Pending claims 24 and 25 are as follows,

24. *A method of specifically inhibiting the activity of Factor Xa, comprising contacting the factor Xa with the compound of claim 1.*
25. *A method of specifically inhibiting the activity of Factor Xa, comprising contacting the factor Xa with the compound of claim 2.*

Regarding the §112, first paragraph rejection, Applicants respectfully submit that claims 24 and 25 are fully described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants note that the Office action does not indicate whether the enablement rejection is directed to the "use" or to the use as applied to the "myriad of compounds." Regardless, Applicants respectfully submit the specification fulfills the statutory requirements as to the two possible avenues for the rejection.

The method of use for the present invention is taught throughout the specification, for example at page 44, line 19 to line 34 the specification teaches dosage for use of the compounds of the present invention; at page 45, line 1 to page 46, line 9 the specification teaches administration and pharmaceutical compositions directed to administration of the compounds of the present invention.

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Regarding the number of compounds, the specification teaches over 400 compounds that were prepared and biologically screened that specifically inhibit the activity of factor Xa. For example, compounds are taught in Example XXXV (Table 3), Table 2 at page 42, line 17; Example XXXVI (Table 3); Example XXXVIII and Example XXXIX.

The specification teaches compounds that specifically inhibit Factor Xa activity, where the compounds have either the amino acids tyrosine, isoleucine and arginine, that is "YIR", or their equivalent. The compounds that are referenced above that are taught in the specification exemplify various equivalent substitutions that can be made for "YIR", while still maintaining desired activity. The compounds teach that any single amino acid within "YIR" can be substituted, as well as in combination. For example in Table 3, page 78, the taught compounds show that for "Y" or tyrosine can be substituted by equivalent moieties, such as, substituted tyrosines p 79, lines 22 to 29; substituted phenylalanine ("F"), page 80, lines 5 to 15; and pAph (p-amidinophenylalanine), this just recites a few of the many taught equivalent substitutions. Similarly, inspection of the taught compounds listed above will show that Applicants have taught equivalent substitutions for "I" and "R". Applicants respectfully submit that the specification fully supports the breadth of the claimed invention.

Regarding the §112, second paragraph rejection, Applicant respectfully submits that claims 24 and 25 are not indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

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invention. Claims 24 and 25 are directed to "a method of specifically inhibiting the activity of Factor Xa, comprising contacting the factor Xa with the compound of claim . . .". Applicants respectfully submit that all of the elements of the claims are distinctly described and taught in the specification.

The term "activity of Factor Xa" is taught in the specification at page 14, line 25. For example, the specification teaches that the term refers to the ability of factor Xa, by itself or in the assembly of subunits known as the prothrombinase complex to catalyze the conversion of prothrombin to thrombin.

The term "inhibition" is taught in the specification at page 14, line 29. For example inhibition is taught to include both the direct and indirect inhibition of factor Xa activity with teachings of how it acts.

The term "specific" is taught at page 15, line 6 to line 14. For example, the specification teaches that the term "specific" refers to the compounds of the present invention inhibiting the activity of factor Xa without substantially inhibiting the activity of other specified proteases, including plasmin and thrombin. The specification also teaches the procedure used to make this determination in Example XXXVII at page 87.

In summary, Applicants submit that claims 24 and 26 meet the requirements of 35 U.S.C. 112, first and second paragraphs, and urge the removal of the present rejections.

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Double Patenting Rejection

Applicants note the pending double rejection of claim 11, and respectfully submit that said rejection should be held in abeyance until such time all substantive prosecution matters are completed.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he/she is invited to call Cathryn Campbell or the undersigned attorney.

Respectfully submitted,

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Date

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